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STATE OF THE ART

Impact of adverse pregnancy outcomes on brain vascular health and cognition

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Abstract

A State of the Art lecture titled "Impact of Adverse Pregnancy Outcomes on Brain Vascular Health and Cognition" was presented at the International Society on Thrombosis and Haemostasis Congress in 2023. Adverse pregnancy outcomes, encompassing conditions such as gestational hypertension, eclampsia, preeclampsia, preterm birth, fetal growth restriction, stillbirth, and gestational diabetes, may form part of an underrecognized pathway from early adulthood reproductive health factors to later-life vascular cognitive impairment and dementia in women. Adverse pregnancy outcomes are caused by dysregulated vascular and metabolic adaptations during pregnancy, and these pathophysiological changes may persist after delivery. Adverse pregnancy outcomes may contribute to the increased risk of cognitive impairment and dementia directly through vascular and metabolic dysregulation and subsequent development of cardiovascular diseases, or other biological processes may be at play, such as shared maternal risk factors. Extensive epidemiologic evidence has shown that many cognitive impairment and dementia cases may be prevented or delayed by strategies targeting midlife cardiovascular health. Despite the recognized importance of adverse pregnancy outcomes for cardiovascular health, the literature on associated long-term health outcomes is limited. In this State of the Art review article, we summarize the current epidemiologic evidence on the relationship between adverse pregnancy outcomes and cognitive impairment and dementia and provide an overview of the potential pathophysiological mechanisms. Finally, we summarize relevant new data on this topic presented during the 2023 International Society on Thrombosis and Haemostasis Congress.

KEYWORDS
cardiovascular disease, dementia, eclampsia, preeclampsia, pregnancy outcome

Essentials

- Pregnancy complications may increase maternal risk of brain problems in later life.
- Eight original studies have explored pregnancy complications and maternal brain health.
- The evidence is strongest for hypertension during pregnancy, a common pregnancy complication.
- Available studies are limited, and many areas of uncertainty remain.

TABLE 1 Definitions of adverse pregnancy outcomes.

Adverse pregnancy outcome	Definition	Pathophysiological mechanism
Gestational hypertension	New hypertension that develops after week 20 of pregnancy without proteinuria [5].	Placental dysfunction; lower placental growth factors; angiogenic imbalance
Preeclampsia	New hypertension that develops after week 20 of pregnancy, with proteinuria or evidence of end-organ dysfunction [5].	
Eclampsia	The new onset of seizures or coma in a pregnant woman with preeclampsia [6].	
Preterm birth	Spontaneous or medically induced birth before 37 wk gestational age [7].	Multifactorial, placental dysfunction is common
Fetal growth restriction	The fetus does not reach its biological growth potential [8].	
Stillbirth	Loss of a fetus at or after 28 wk of pregnancy but before or during labor[a] [9].	
Gestational diabetes	Diabetes develops during pregnancy in females without an existing diagnosis of diabetes [10].	β-cell dysfunction on a background of chronic insulin resistance during pregnancy

[a]As defined by the World Health Organization. The Centers for Disease Control and Prevention in the United States defines stillbirth as loss of a fetus at or after 20 weeks of pregnancy [9].

1 | INTRODUCTION

Adverse pregnancy outcomes may form part of an underrecognized pathway from early adulthood reproductive health factors to Alzheimer's disease (AD) and related dementias. Vascular dementia (VaD) is the second most prevalent cause of dementia after AD. Unlike AD, VaD can develop due to a wide range of conditions that affect cerebral blood vessels, and memory impairment is often not the first symptom [1]. Underlying vascular pathologies contributing to VaD include multiple lacunar infarcts, white matter lesions, strategic infarcts, hypoperfusion with border zone ("watershed") infarcts, and hemorrhagic lesions [1]. Recognizing the diverse nature of vascular pathologies and the spectrum of cognitive deficits VaD presents, the term vascular cognitive impairment and dementia (VCID) is commonly used to encompass this heterogeneity [2,3].

While adverse pregnancy outcomes are recognized as a risk-enhancing factor for cardiovascular disease [4], the impact of adverse pregnancy outcomes on vascular cognitive impairment risk in those who have given birth is less clear. Adverse pregnancy outcomes, such as hypertensive disorders of pregnancy, preterm birth, fetal growth restriction, stillbirth, or gestational diabetes, affect 1 in 5 pregnancies in the United States (Table 1) [5–12]. Adverse pregnancy outcomes are a result of dysregulated vascular and metabolic adaptations during pregnancy, and these pathophysiological changes may persist after delivery [13].

Adverse pregnancy outcomes may contribute to maternal VCID risk through biological processes such as vascular endothelial dysfunction and neuroinflammation, ultimately promoting associated cognitive decline. In addition, adverse pregnancy outcomes and VCID may share maternal risk factors, such as genetic variants, obesity, or physical inactivity, that may predispose to both conditions (Figure 1) [3,14,15]. While the contribution of vascular pathology to the development of VCID is widely acknowledged, emerging evidence shows that vascular changes may play an important role in neurodegeneration and the subsequent development of AD [16,17]. A few studies have reported an association between the history of hypertensive disorders of pregnancy and AD, providing further support for this notion [18,19].

In this State of the Art review article, we summarize the current epidemiologic evidence on the relationship between adverse pregnancy outcomes and VCID and highlight gaps in the research. As a narrative review, this article aims to recapitulate the points made at the author's (E.M.) State of the Art lecture at International Society on Thrombosis and Haemostasis (ISTH) 2023 and give a brief synopsis of new relevant research presented at the Congress. This is not intended as a systematic review and includes the perspective of the authors. While we focus primarily on VCID, a broad term that encompasses a spectrum of cognitive impairments associated with vascular neuropathology, we also briefly discuss other types of dementia to capture the heterogeneity and complexity of cognitive impairment that may stem from vascular causes. When referencing results from previous studies, we adhere to the original language related to sex and gender as reported in those studies. For the narrative portions of our article, where we present our own perspectives, we use nongendered language to maintain a broader approach.

2 | EPIDEMIOLOGY

Despite the recognized importance and relatively high occurrence of adverse pregnancy outcomes among those who have given birth, the literature on incidence and temporal trends of adverse pregnancy outcomes is limited. Globally, preeclampsia is estimated to affect 2% to 8% of pregnancies, and gestational hypertension is estimated to affect 2% to 3% of pregnancies [20,21]. A study from the United States reported that during the period between 1987 and 2004, the

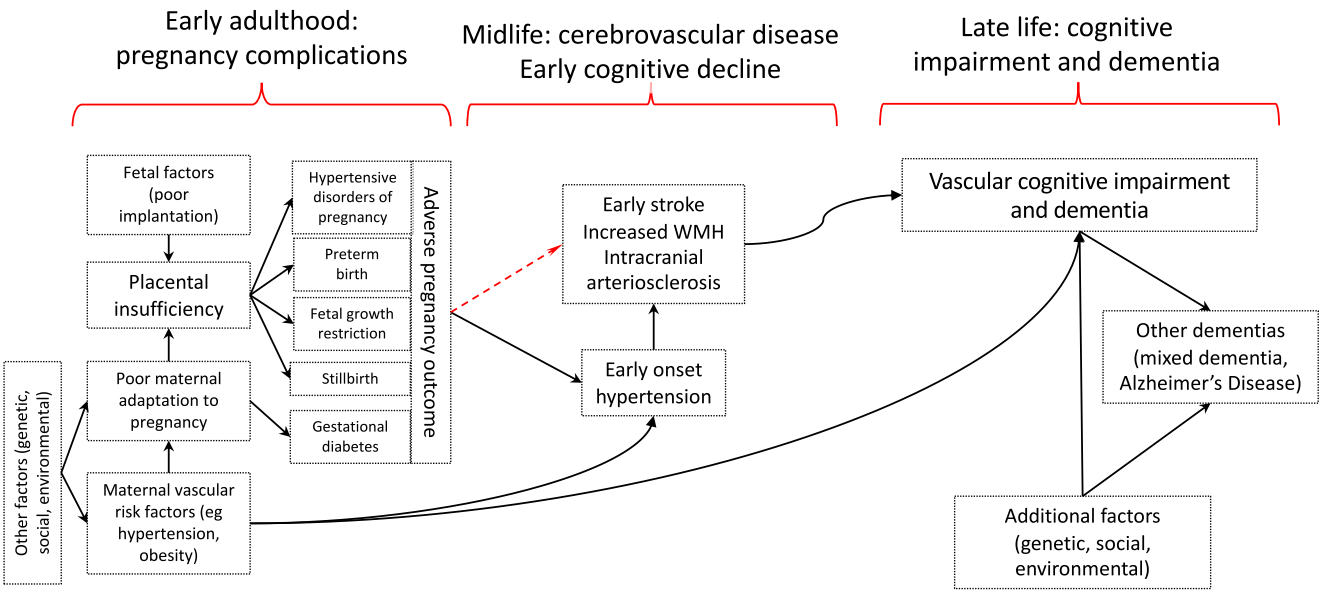

FIGURE 1 Potential direct and indirect effects of adverse pregnancy outcomes, along with possible confounders and mediators, illustrate the complexity of characterizing pathways from adverse pregnancy outcomes to cognitive impairment and dementia. WMH, white matter hyperintensities.

incidence of preeclampsia increased by 25%, the incidence of gestational hypertension tripled, and the incidence of eclampsia decreased by 22% [20]. The prevalence of gestational diabetes in the United States has increased from 0.3% in 1979-1980 to 5.8% in 2008-2010, reaching 8% in 2016 [22,23]. It is possible that these changes may reflect improvements in screening practices and revisions of diagnostic criteria in addition to true trends. Epidemiologic data on fetal growth restriction, also known as intrauterine growth restriction, are even less precise due to a current lack of consensus on diagnostic criteria. It is estimated that fetal growth restriction affects around 5% to 15% of pregnancies [24]. Data on preterm birth (birth before 37 weeks gestational age) and stillbirths are relatively more precise, although historical changes to classifications make comparisons of trends over time challenging. Among those who gave birth in 2021 in the United States, the preterm birth rate for all births was 10%, and the preterm birth rate for singleton births was only 8.8%, the highest levels since 2007 [25]. The late fetal mortality rate, or stillbirth rate, defined as the number of babies born with no signs of life at 28 weeks or more of gestation, was 2.8 per 1000 total births in 2020 [26]. The total fetal mortality rate in the United States has decreased by 23% since 1997, while maternal mortality has increased [26].

A scientific statement from the American Heart Association highlights the link between adverse pregnancy outcomes and the increased risk of cardiovascular morbidity and mortality in those who have given birth, emphasizing the importance of early identification, risk assessment, and targeted interventions to mitigate the long-term consequences of adverse pregnancy outcomes [4]. A substantial body of evidence supports that hypertensive disorders of pregnancy are associated with a higher risk of cardiovascular diseases and cardiovascular mortality [27–29]. Although the evidence supporting the association between other adverse pregnancy outcomes and cardiovascular risk is relatively more modest, emerging studies increase confidence in these findings. For example, preterm birth was found to be associated with an increased risk of hypertension in later life [30], along with an increased risk of cardiovascular diseases, including coronary heart disease and cardiovascular death [31,32]. Some evidence also suggests an increased risk of cardiac dysfunction and poor cardiac reserve in women with fetal growth-restricted pregnancies [33].

Stroke is a key cardiovascular risk factor for developing VCID. Experiencing at least 1 adverse pregnancy outcome was found to be associated with younger age at the onset of stroke, and experiencing multiple adverse pregnancy outcomes shortened the time to stroke onset [34]. Experiencing adverse pregnancy outcome increases the overall risk of stroke. For example, women with hypertensive disorders of pregnancy had 1.7 times the rate of stroke for up to 17 years after pregnancy compared to those without hypertensive disorders of pregnancy [35]. Women who had a singleton delivery during 1973-2015 in Sweden had a higher risk of stroke after preterm birth up to 43 years after delivery [36]. Further, in a cohort comprising 7 developed countries, those who had experienced stillbirth had 1.3 times the rate of nonfatal stroke and 1.2 times the rate of fatal stroke [37]. These findings are consistent with meta-analyses of 18 studies, wherein women with stillbirth had 1.4 times the rate of stroke compared to those without stillbirth [38].

3 | CURRENT EVIDENCE

Most of the current literature focuses on hypertensive disorders of pregnancy, whereas the effect of other adverse pregnancy outcomes on VCID remains largely unexplored. We identified 8 original studies and 2 meta-analyses that we discuss in further detail (Table 2) [39–46]. We focus primarily on VaD as the outcome; however, we

TABLE 2 Selected studies.

Study	Type	Outcomes	Exposure	Data source	Country	Sample size	Length of follow-up	Estimates
Schliep et al. [39]	Systematic review	Dementia	Hypertensive disorders of pregnancy and subtypes: gestational hypertension, preeclampsia/eclampsia, or other/unspecified hypertensive disorders of pregnancy	5 cohort studies	Netherlands, Denmark, United States, Sweden	2,493,579	-	-
Samara et al. [40]	Systematic review	Vascular dementia, Alzheimer's disease, and dementia of any type	History of preeclampsia	3 cohort studies	Sweden, Denmark	2,309,946	-	-
Basit et al. [19]	Retrospective cohort	Dementia, Alzheimer's disease, vascular dementia, other dementia (ICD codes)	History of preeclampsia defined as registered with preeclampsia, eclampsia, or hemolysis, elevated liver enzymes, and low platelets syndrome (ICD codes)	National registers (Danish Civil Registration System, Medical Birth Register, National Patient Register, Causes of Death Register)	Denmark	1,178,005	From 1978 to 2017; median follow-up 21.1 (IQR, 11.3-23.4) y	The risk of VaD in women with a history of preeclampsia: HR, 3.46 (95% CI, 1.97-6.10)
Basit et al. [41]	Retrospective cohort	Dementia, Alzheimer's disease, vascular dementia, other dementia (ICD codes)	Miscarriage is defined as a missed abortion or spontaneous abortion registered between 7 and 22 wk of completed gestation. Stillbirth is defined as a pregnancy loss occurring after 28 wk in the period 1977-2003 and after 22 wk in the period 2004-2015 or a miscarriage in gestational week 23-28.	National registers (Danish Civil Registration System, Medical Birth Register, National Patient Register, Causes of Death Register, National Prescription Register)	Denmark	1,243,957	From 1977 to 2017; median follow-up 21.6 (IQR, 11.6–23.4) y	The risk of VaD in women with a history of: - One miscarriage: HR, 1.14 (95% CI, 0.71-1.85) - Two or more miscarriages: HR, 2.24 (95% CI, 1.14-4.39) - Stillbirth: HR, 2.29 (95% CI, 0.56-9.31)

(Continues)

TABLE 2 (Continued)

Study	Type	Outcomes	Exposure	Data source	Country	Sample size	Length of follow-up	Estimates
Adank et al. [42]	Retrospective cohort	Executive function, processing speed, verbal memory, motor function, visuospatial ability, global cognition factor (g-factor)	Hypertensive disorder of pregnancy (gestational hypertension [systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg without proteinuria after 20 wk of gestation in previously normotensive women], preeclampsia [a new onset of hypertension with systolic blood pressure ≥140 mm Hg] or diastolic blood pressure ≥90 mm Hg and proteinuria [≥300 mg/d] at or after 20 wk of gestational age).	ORACLE study embedded within the Generation R Study	Netherlands	596	Delivery date between 2002 and 2006; median follow-up 14.1 (90% range, 13.6-15.7) y	Immediate recall: b = −0.25 (95% CI, −0.44 to −0.06) Delayed recall: b = −0.30 (95% CI, −0.50 to −0.10)
Wang et al. [18]	Retrospective cohort	Diagnosis of dementia based on DSM-IV; diagnosis of Alzheimer's disease based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (for definite, probable, or possible Alzheimer's disease)	Preeclampsia was evaluated by a questionnaire (yes/no).	Framingham Offspring Study	United States	1249	Median follow-up 12 (IQR, 7-21) y	The risk of all-cause dementia in women with a history of preeclampsia: HR, 1.56 (95% CI, 1.03-2.15)

(Continues)

TABLE 2 (Continued)

Study	Type	Outcomes	Exposure	Data source	Country	Sample size	Length of follow-up	Estimates
Andolf et al. [43]	Retrospective cohort	Dementia, vascular dementia, Alzheimer's disease (ICD codes)	Abruptio placentae, preeclampsia, placental anomaly, preterm labor and birth, recurrent miscarriages, fetal growth restriction, intrauterine excessive growth, infertility, intrauterine fetal death, preterm premature rupture of membranes, pregnancy-induced hypertension, gestational diabetes (ICD codes)	National registers (Medical Birth Register, National Patient Register, Cause of Death Register, Multi-generation Register, Total Population Register, Education Register, 1970 Population and Housing Census)	Sweden	1,128,709	Delivery date between 1973 to 1993. Followed up until 2013.	The risk of VaD in women with: - pregnancy-induced hypertension: HR, 1.88 (95% CI, 1.32-2.69) - preeclampsia: HR, 1.63 (95% CI, 1.23-2.16) - spontaneous preterm labor and birth: HR, 1.65 (95% CI, 1.12-2.42) - preterm premature rupture of membranes: HR, 1.60 (95% CI, 1.08-2.37)
Andolf et al. [44]	Retrospective cohort	Vascular dementia, dementia (ICD codes)	Hypertension without proteinuria, hypertension and proteinuria, mild preeclampsia, severe preeclampsia or eclampsia, unspecified preeclampsia (ICD codes)	National registers (Medical Birth Registry and the Total Population Registry)	Sweden	284,598	Diagnosis between 1973 and 1975	The risk of VaD in women with previous hypertensive disorder of pregnancy: HR, 1.05 (95% CI, 0.33-3.34) The risk of VaD in women with hypertension and proteinuria: HR, 6.27 (95% CI, 1.65-27.44)
Nelander et al. [45]	Ambispective cohort	Dementia (ICD codes)	Categories based on the questionnaire: no hypertension; preeclampsia; gestational hypertension; high blood pressure and unclear proteinuria; and do not know.	Screening Across the Lifespan Twin study (participants retrieved from the nationwide Swedish Twin Register,	Sweden	3232	Inclusion between 1998 and 2002, follow-up until the end of 2010	The risk of dementia in women with any hypertensive disorder of pregnancy: HR, 1.19 (95% CI, 0.79-1.73)

(Continues)

TABLE 2 (Continued)

Study	Type	Outcomes	Exposure	Data source	Country	Sample size	Length of follow-up	Estimates
				linked with the National Patient Register and the Cause of Death Register)				
Fields et al. [46]	Case-control study	Consensus panel diagnosis of mild cognitive impairment based on attention, working memory, psychomotor processing speed, executive functioning, language, perceptual processing, learning, and memory tests (no cognitive impairment, MCI-single domain, MCI-multiple domains, dementia)	Preeclamptic pregnancy between 1976 and 1982 that met the standard definition: 1) 2 or more blood pressure readings of a systolic blood pressure >140 mm Hg or a diastolic blood pressure >90 mm Hg at least 4 h apart after 20 wk gestation and 2) new onset proteinuria, as defined by a urine dipstick 1+, or proteinuria 0.300 g per 24 h, or a protein-to-creatinine ratio equivalent to 0.300 g per 24 h. Emergency.	Rochester Epidemiologic Project medical records-linkage system	United States	80	Pregnancy from 1976 to 1982, 35-40 y of follow-up	Pattern of cognitive impairment in women with hypertensive disorders of pregnancy compared to women with normotensive pregnancy: *P* for trend = .03

DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; HR, hazard ratio; ICD, International Classification of Diseases; MCI, mild cognitive impairment; ORACLE, Origins of Alzheimer's Disease Across the Life course; VaD, vascular dementia.

note that it is not always possible to differentiate a specific type of dementia, and not all studies distinguished the type of dementia due to a small number of participants with VaD.

The first study performed on data from Swedish registries investigated the relationship between hypertensive disorders of pregnancy using a sample of 284,598 women who gave birth between 1973 and 1975 [44]. No association between hypertensive disorders of pregnancy and VaD or any dementia in later life was reported, except for an increased risk of VaD after diagnosis of hypertension and proteinuria in pregnancy (hazard ratio [HR], 6.27; 95% CI, 1.65-27.44) [44]. This study was limited by a relatively small number of women affected by hypertensive disorders of pregnancy and potential misclassification due to an unreliable definition of preeclampsia in the specific time period under investigation [44]. Another study that investigated all-cause dementia included 3232 women from Sweden and found no association between hypertensive disorders of pregnancy and subsequent risk of dementia; however, women with a history of hypertensive disorders of pregnancy had 1.36 times the rate of stroke (95% CI, 1.00-1.81) compared with women with no history of hypertensive disorder of pregnancy [45]. The major limitation of this study was the reliance on self-reported data of the history of a hypertensive disorder of pregnancy, which was collected decades after the occurrence of the index event and was likely to suffer from a recall bias [45].

To further expand on the research, a subsequent registry-based analysis was conducted on a larger sample of 1,128,709 Swedish women who gave birth between 1973 and 1993 and were followed until 2013 [43]. This extended study investigated the relationship between several adverse pregnancy outcomes, including hypertensive disorders of pregnancy, fetal growth restriction, preterm birth, gestational diabetes, preterm premature rupture of membranes, abruptio placentae, late miscarriages, and the risk of later-life

dementia [43]. The findings indicated that gestational hypertension (HR, 1.88; 95% CI, 1.32-2.69), preeclampsia (HR, 1.63; 95% CI, 1.23-2.16), preterm birth (HR, 1.65; 95% CI, 1.12-2.42), and preterm premature rupture of membranes (HR, 1.60; 95% CI, 1.08-2.37) were associated with an increased risk of VaD, even when adjusted for cardiovascular diseases, whereas experiencing other adverse pregnancy outcomes was not associated with VaD [43]. There was no association between non-VaD and any adverse pregnancy outcome [43].

Another registry-based study from Denmark found that those with a history of preeclampsia had 3.46 times the rate of VaD (95% CI, 1.97-6.10), even when adjusted for prevalent cardiovascular diseases, whereas the risk of non-VaDs was only slightly increased [19]. The cohort included 1,178,005 women who gave birth between 1978 and 2015. Although the diagnosis of dementia tends to be underreported in the registry databases, the findings from registry-based studies are likely generalizable to the population of Denmark due to the inclusion of all women who gave birth during the period of interest [19]. On the other hand, it is important to acknowledge the potential for misclassification bias in registry-based studies, as the sensitivity of diagnosing preeclampsia in the Swedish National Patient Register was 69%, while the specificity reached 99% [43].

These findings were consistent with results from the 2 identified meta-analyses. The first meta-analysis considered all hypertensive disorders of pregnancy and found an increased rate of dementia (HR, 1.38; 95% CI, 1.18-1.61) and VaD (HR, 3.14; 95% CI, 2.32-4.24) [39]. The second meta-analysis focused on the history of preeclampsia and gestational hypertension separately [40]. Although this study did not find any association between both hypertensive disorders of pregnancy and dementia of any type, a history of preeclampsia was associated with an increased rate of VaD (HR, 2.60; 95% CI, 2.03-3.33) [40].

Only one study investigated the risk of dementia after stillbirth. The study was based on data from Danish national registers and found that women with a history of stillbirth had a higher rate of dementia (HR, 1.86; 95% CI, 1.28-2.71) compared with other women, while the rate of VaD was higher only among women who were 65 years old or older, and the level of uncertainty was high (HR, 7.40; 95% CI, 1.77-33.0) [41]. The history of stillbirth was defined as the loss of a fetus after 28 weeks of pregnancy in the period 1977-2003 and after 22 weeks in the period 2004-2015 [41]. The study included 1,243,957 women who were followed for 21,672,433 person-years; however, the cohort was young, and the median age at the end of follow-up was 49 years, with 10% of women reaching the age of 65 [41].

Finally, one study focused on the risk of dementia in those who had gestational diabetes [47]. The study used Mendelian randomization approach and concluded that gestational diabetes and dementia are not causally associated [47]. However, this study also did not find any relationship between high body mass index, heart disease, and dementia, suggesting that other factors, such as lack of power or misclassification bias, might play a role in these negative findings [47,48].

Diagnosis of dementia is a binary outcome determined by a physician and is characterized by cognitive decline severe enough to disrupt the ability to perform everyday activities [49]. However, cognitive decline may start earlier in life and may never fully develop into dementia [49]. A small population-based study focused on cognitive functions in mothers 15 years after pregnancy [42]. In a cohort of 596 women who lived in Rotterdam and gave birth between 2002 and 2006, women with a history of hypertensive disorder of pregnancy had poorer working memory and verbal learning 15 years after pregnancy [42]. Another study based on medical registry data linked to population-based data from the Rochester Epidemiologic Project explored cognition in women 35 years after pregnancy [46]. Forty women who had a history of preeclampsia were matched based on age and parity with 40 women who had experienced a normotensive pregnancy, and their risk of cognitive impairment was compared [46]. While the study reported no differences in cognitive test scores, women with a history of preeclampsia were more likely to receive a diagnosis of mild cognitive impairment and had more cognitive domains affected, particularly executive dysfunction and verbal list learning impairment [46].

The current evidence is mostly based on data from national registers and health care records, leaving a potential for misclassification bias. Dementia is often underdiagnosed [50], which might lead to underestimation of the effect. VaD is especially often misdiagnosed, and previous studies rely mostly on clinical diagnosis of VaD and lack information on structural correlates and other biomarkers of VaD years after experiencing adverse pregnancy outcomes. Registry-based studies are also subject to limited generalizability due to differences in healthcare practices across regions and over time. Additionally, the diagnosis of dementia might be preceded by decades of cognitive decline. However, only 2 small studies used data with measurements of cognition [42,46].

Despite these limitations, there is a body of evidence suggesting that adverse pregnancy outcomes are associated with worse cognition later in life and with a higher risk of dementia. Although data on less common types of dementia remain limited, this relationship appears to be stronger for VaD compared with all-cause dementia or AD.

4 | PATHOPHYSIOLOGY

It is biologically plausible that common pathways involving angiogenic imbalance, endothelial inflammation, and cerebral microangiopathy link pathophysiological processes involved in both adverse pregnancy outcomes and vascular cognitive impairment. In addition, some of the same pathways have been implicated in Alzheimer's pathology, as summarized here.

4.1 | Placental disorders and vascular cognitive impairment

Several adverse pregnancy outcomes, including gestational hypertension, preeclampsia, preterm birth, and fetal growth restriction, are thought to reflect underlying placental dysfunction. These disorders

often occur concurrently and show similar pathophysiological features [51]. Potential pathways from placental bed disorders to maternal vascular cognitive impairment include several shared biological processes, such as angiogenic dysregulation, neuroinflammation, and cerebral microangiopathy (Figure 2).

A critical pathophysiological feature of these disorders is angiogenic imbalance. The proangiogenic factor placental growth factor (PlGF), a member of a family of vascular endothelial growth factors, is normally elevated in pregnancy and plays an essential role in the regulation of the maternal immune response to trophoblast implantation and placental vascular development [52]. PlGF creates an environment that supports immune tolerance, angiogenesis, and balance between inflammatory and anti-inflammatory processes, all of which are needed for normal placental implantation and subsequent sustenance of the developing embryo [52,53].

The serum concentration of PlGF is decreased in women with placental dysfunction, likely as a result of downregulated expression of PlGF and increased binding of PlGF to soluble fms-like tyrosine kinase-1, a soluble form of the vascular endothelial growth factor receptor, which is overexpressed in affected women [53]. The imbalance of the angiogenic factors soluble fms-like tyrosine kinase-1 and PlGF during pregnancy is on the causal pathway to preeclampsia [54] and is similarly central to the pathophysiology of other placentally mediated adverse pregnancy outcomes [55–57]. "Placental failure" may itself lead to long-term vascular endothelial damage; alternatively, placental dysfunction may be a marker of overall maternal vascular risk [58]. Interestingly, angiogenic dysregulation is also now recognized to play a key role in the pathogenesis of cerebral small vessel disease, with PlGF recently recognized as a reliable and sensitive biomarker for VCID [59,60]. One of the consequences of angiogenic dysregulation is endothelial dysfunction, precipitating the release of proinflammatory cytokines and stimulating oxidative stress [61]. Systemic inflammation may lead to dysfunction of the neurovascular unit and blood-brain barrier, allowing toxins, immune cells, and inflammatory molecules to permeate the brain and cause neuroinflammation [61]. It is plausible that the systemic angiogenic dysregulation and widespread endothelial dysfunction seen in placentally mediated adverse pregnancy outcomes may persist, eventually resulting in cerebral small vessel disease, vascular cognitive impairment, and dementia.

4.2 | Gestational diabetes and vascular cognitive impairment

Gestational diabetes is caused by a dysfunction of pancreatic β-cells on a background of chronic insulin resistance during pregnancy [10]. Although gestational diabetes has a different etiology than adverse pregnancy outcomes that are related primarily to placental dysfunction, these disorders share some pathophysiological features, such as inflammation and endothelial dysfunction, and the placenta may play a role in mediating the maternal inflammatory response to gestational diabetes [62,63]. Further, those who develop gestational diabetes have an increased risk of additional adverse pregnancy outcomes, including preterm birth [64] and hypertensive disorders of pregnancy [65].

4.3 | Possible pathways to AD

While the link between adverse pregnancy outcomes and AD is less clear, several plausible mechanisms could connect adverse pregnancy outcomes with the risk of AD. First, experiencing an adverse pregnancy outcome is associated with a 2-fold increased risk of atherosclerotic cardiovascular disease later in life [66] and 60% to 80% increased risk of heart failure [67]. Cardiovascular conditions may lead to a higher risk of AD through cerebral hypoperfusion, which causes acidosis and oxidative stress and ultimately reduces autophagy and stimulates the formation of hyperphosphorylated tau, a hallmark of AD pathology [68,69]. Second, it is possible that adverse pregnancy outcomes and AD share common causes. For example, genetic and epigenetic changes in the *STOX1* gene are associated with both preeclampsia and late-onset AD [70]. Lastly, in addition to its strong correlation with vascular cognitive impairment, as summarized above, PlGF has also recently been positively correlated with Alzheimer's pathology, including higher Braak neurofibrillary tangle stage, higher Consortium to Establish a Registry for Alzheimer's Disease (CERAD) scores, and more AD neuropathologic change [71].

5 | ISTH 2023 CONGRESS REPORT

Many of the concepts discussed in this article were presented in the State of the Art lecture, "Impact of Adverse Pregnancy Outcomes on Brain Vascular Health and Cognition," at the ISTH 2023 Congress in Montreal, Canada. While no scientific abstracts on this specific topic were presented at the Congress, a few abstracts may provide insight into the pathways involved in adverse pregnancy outcomes that could contribute to vascular cognitive impairment. Horn et al. [72] analyzed functional assays of coagulation factors in women with a history of preterm preeclampsia compared with women with a history of normotensive pregnancy and nulliparous women. They found that those with a history of preterm preeclampsia showed differences in hemostatic profiles, suggesting that hemostatic changes seen in the acute setting in patients with preeclampsia could have long-term effects. López et al. [73] demonstrated that circulating placenta-derived extracellular vesicles and neutrophil extracellular traps in sera were potential causal factors in preeclampsia-associated endothelial damage, triggering an oxidative, prothrombotic, and proinflammatory state that could potentially contribute to long-term sequelae. Lastly, Kenny et al. [74] offered a novel, machine learning–based method aimed at differentiating pregnancy phenotypes, including preeclampsia, based on circulating extracellular vesicle profiles, potentially providing a new

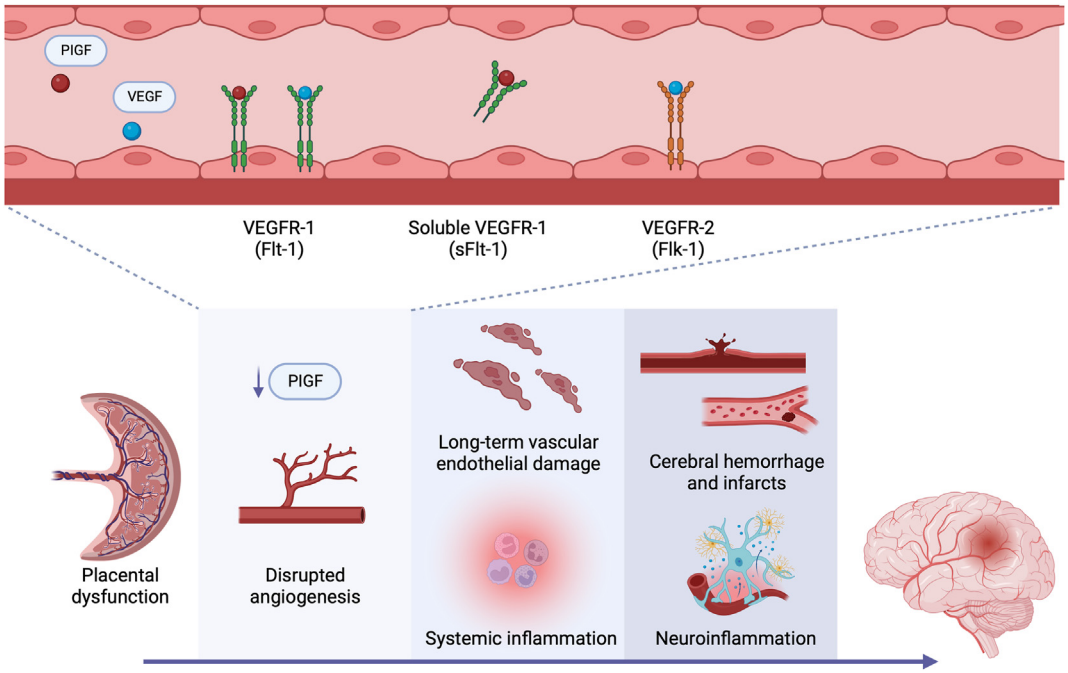

FIGURE 2 Potential pathways from placental bed disorders to maternal vascular cognitive impairment include biological processes such as angiogenic dysregulation, neuroinflammation, and cerebral microangiopathy. Lower placental growth factor (PlGF) levels in pregnancy are associated with adverse pregnancy outcomes; conversely, higher PlGF levels later in life are associated with vascular cognitive impairment and dementia. Flk-1, fetal liver kinase-1; Flt-1, fms-like tyrosine kinase-1; sFlt-1, soluble fms-like tyrosine kinase-1; VEGF, vascular endothelial growth factor; VEGFR-1, vascular endothelial growth factor receptor 1. Created with BioRender.com.

tool to help identify pathophysiological pathways involved in adverse pregnancy outcomes.

6 | FUTURE DIRECTIONS

Most existing aging cohorts lack meticulously phenotyped, prospectively collected pregnancy data and thus have limited ability to investigate the effects of adverse pregnancy outcomes on maternal VCID risk and the pathways that underlie this relationship. While there is a growing body of evidence on the role of hypertensive disorders of pregnancy in the increased risk of VCID in individuals who have been pregnant, data on other adverse pregnancy outcomes are largely lacking. Further, future studies should aim to collect data on specific types of dementia and ideally support the clinical diagnosis by structural markers and biomarkers.

Importantly, most studies were conducted in high-income countries of Northern Europe and in the United States. There are considerable variations in the prevalence of adverse pregnancy outcomes between countries and regions. Within the European context, the estimated prevalence of gestational diabetes is 31.5% in Eastern Europe and 8.9% in Northern Europe [75], and the stillbirth rate per 1000 births varies between 2.0 in Finland and 4.9 in Latvia and France [76]. Thus, findings from current studies may not be generalizable to other populations, and the risk of VCID following adverse pregnancy outcomes might be underestimated.

Further, the relationship between adverse pregnancy outcomes and VCID risk might substantially vary within countries due to differences in risk profiles based on demographic and social characteristics. For example, Black pregnant individuals experience disproportionate rates of adverse pregnancy outcomes, regardless of their socioeconomic status [11,12]. The current studies are limited by the inclusion of mostly White populations. There is an urgent need for rigorous, multiracial, and multiethnic studies investigating sex-specific risk factors, including adverse pregnancy outcomes, on dementia in individuals who have been pregnant. This was highlighted in a recent consensus statement from the Society for Women's Health Research Interdisciplinary Network on Alzheimer's Disease [77].

The incidence of adverse pregnancy outcomes is high, and extensive epidemiologic evidence has linked adverse pregnancy outcomes with worse long-term cardiometabolic outcomes. Emerging evidence suggests that those who have experienced adverse pregnancy outcomes may face a higher risk of VCID in later life, although the underlying pathways remain largely unexplored. Currently, there is no cure for dementia, and preventive strategies are a priority to mitigate the burden of cognitive disorders in later life. The identification of risk factors occurring in early adulthood and midlife is an essential step in these efforts, offering potential pathways for early interventions. Preconception, pregnancy, and postpartum care may become an important pillar in the primary prevention of cognitive decline, but currently available evidence is limited, and many areas of uncertainty remain.

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AUTHOR CONTRIBUTIONS

K.W. performed the literature review and drafted sections of the manuscript. E.M. conceived the manuscript, wrote sections of the manuscript, and revised the entire manuscript. Both authors take full responsibility for the content of the manuscript.

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